

The beginning of the end of warfarin?

Randomised trials suggest that ximelagatran is “non-inferior” to warfarin for preventing stroke in patients with non-valvular atrial fibrillation, but important questions remain

ATRIAL FIBRILLATION is a strong and independent risk factor for stroke because it predisposes to thrombus formation in the left atrial appendage, and subsequent embolism to the brain.¹ Each year, at least 6000 cardioembolic ischaemic strokes occur among an estimated 150 000 Australians with atrial fibrillation,^{2,3} and these numbers are expected to rise substantially with the ageing of the Australian population and associated increase in the prevalence of atrial fibrillation.

The only two treatments proven to reduce the risk of stroke among patients with atrial fibrillation are aspirin and adjusted-dose warfarin.⁴ However, both have limitations. Aspirin is only modestly effective, reducing the risk of stroke by about a fifth compared with placebo (absolute risk reduction [ARR], 1.7% per year; number of patients needed to treat for one year to prevent one stroke [NNT], 59). Warfarin reduces the risk of stroke by about two-thirds compared with placebo (ARR, 3.1% per year; NNT, 32) and by about a third compared with aspirin (ARR, 0.8% per year; NNT, 125), but causes at least twice as many intracranial and extracranial bleeds as aspirin, particularly in patients at increased risk of bleeding (eg, those aged over 75 years, those with a history of bleeding; see Box 1).⁴ Warfarin is also inconvenient to use because it has a narrow therapeutic index, interacts with numerous drugs and food, and requires close laboratory monitoring (Box 2).⁵ Consequently, only a third to a half of patients with atrial

fibrillation who are appropriate candidates for warfarin therapy actually receive it.⁶ Reducing the intensity of warfarin therapy to an international normalised ratio (INR) of less than 2.0 lowers the risk of bleeding, but is associated with an increased incidence of ischaemic stroke and worse stroke outcomes compared with standard-intensity warfarin therapy (INR \geq 2.0).⁷

Direct thrombin inhibitors are a new class of anticoagulant drugs that bind directly to thrombin and block its interaction with substrates, thus inhibiting fibrin formation, thrombin-mediated activation of coagulation, and thrombin-induced platelet aggregation. Hirudin is the only direct thrombin inhibitor currently available for use in Australia, but must be given parenterally and is approved only for the treatment of heparin-induced thrombocytopenia. Ximelagatran, a pro-drug of melagatran, is an orally administered direct thrombin inhibitor and the newest drug in this class. It is rapidly absorbed from the gut and converted to its active form, melagatran. Melagatran is not metabolised or bound to plasma proteins. It is cleared predominantly (about 80%) by the kidneys, and has a half-life of 4–5 hours, which means ximelagatran needs to be administered twice daily (Box 2).

Two large phase III randomised trials have recently evaluated ximelagatran as a replacement for warfarin to prevent thrombotic complications in patients with non-valvular atrial fibrillation.^{8,9} The primary objective of the

1: Estimated benefits and risks of treating a typical cohort of 1000 patients with non-valvular atrial fibrillation with aspirin, adjusted-dose warfarin, or ximelagatran*

	Aspirin (v placebo)		Warfarin (v placebo)		Warfarin (v aspirin)		Ximelagatran (v warfarin) [†]	
Stroke [‡]	ARR ↓ 17	NNT 59	ARR ↓ 31	NNT 32	ARR ↓ 8	NNT 125	ARR [§] 0	NNT [§] —
Major extracranial bleeds [¶]	ARI ↑ 1	NNH 1000	ARI ↑ 3	NNH 333	ARI ↑ 2	NNH 500	ARR ↓ 6	NNT 167
ALT \geq 3 times upper limit of normal	—	—	—	—	—	—	ARI ↑ 53	NNH 19

ARR = absolute risk reduction. ARI = absolute risk increase. NNT = number of patients needed to treat for one year to prevent or avoid one event. NNH = number of patients needed to treat for one year to harm by causing one event. ALT = alanine aminotransferase.

* Data for aspirin v placebo, warfarin v placebo, and warfarin v aspirin are adapted from Hart et al.⁴ † ARR and NNT in the SPORTIF trials were calculated by dividing the pooled event rate by the mean duration of follow-up in years (approximately 1.5 years). ‡ Includes haemorrhagic stroke. § Includes stroke and systemic embolism.

¶ Event rates are likely to be substantially higher outside clinical trial settings, in the elderly, and in those with major comorbid conditions.

2: Comparison of the pharmacology and costs of aspirin, adjusted-dose warfarin and ximelagatran to prevent stroke in patients with non-valvular atrial fibrillation

	Aspirin	Warfarin	Ximelagatran
Route	Oral	Oral	Oral
Dose	150–325 mg	Variable*	36 mg
Frequency	Once daily	Once daily	Twice daily
Half-life	20 minutes	40 hours	4–5 hours
Clearance	Systemic	Hepatic	Renal [†]
Laboratory monitoring	Not required	INR	Liver function tests [‡]
Antidote	No	Yes — Vitamin K	No
Reversal of antithrombotic effect	Platelet transfusion	Vitamin K Fresh frozen plasma Prothrombinex	Discontinue ximelagatran Maintain diuresis Haemodialysis
Food interactions	Nil	Multiple	Nil known
Drug interactions	Uncommon	Multiple	Nil known
Major side-effects	Gastrointestinal bleeding	Bleeding	Bleeding Abnormal liver function test results
Precautions and contraindications	Bleeding diathesis Peptic ulcer Allergy	Bleeding diathesis Alcoholism Dementia Impaired liver function	Bleeding diathesis Impaired renal function Impaired liver function
Approximate costs	\$2 per month [§]	\$10 per month [§]	Unknown [¶]

INR = international normalised ratio.

*Dose adjusted according to the results of the INR. †Trials of ximelagatran in atrial fibrillation have been restricted to patients with a creatinine clearance rate of ≥ 30 mL/min. ‡Monitoring of liver function is likely to be required for the first 6 months. §Pharmaceutical Benefits Scheme November 2003: aspirin, \$6.13 for 112 100 mg enteric-coated tablets; warfarin, \$8.40 for 50 5 mg tablets (does not include the cost of laboratory monitoring). ¶Cost of ximelagatran is not known but is likely to be at least \$100 per month for a private prescription.

Stroke Prevention using the ORal direct Thrombin Inhibitor ximelagatran in patients with non-valvular atrial Fibrillation (SPORTIF) III and V trials was to determine whether ximelagatran given in a fixed dose of 36 mg twice daily without laboratory monitoring was *non-inferior* to adjusted-dose warfarin (INR, 2.0–3.0) for the prevention of stroke or systemic embolism in patients with non-valvular atrial fibrillation and at least one additional major risk factor for stroke. The prespecified criterion for non-inferiority required that the lower confidence interval for the difference in the rate of stroke or systemic embolism between ximelagatran and warfarin did not exceed the prespecified threshold of 2% per year.¹⁰ Establishment of non-inferiority would imply that ximelagatran has either equivalent or superior effectiveness to warfarin and would allow clinicians to select ximelagatran over warfarin for convenience or safety.

The design of the two SPORTIF trials was identical, except that SPORTIF III (3407 patients) was conducted in Europe, Asia, Australia and New Zealand and treatment allocation was open label, while SPORTIF V (3922 patients) was conducted in North America and treatment allocation was double blinded.

The pooled results of the SPORTIF III and V trials (which had mean follow-up periods of 17 or 20 months, respectively) showed no significant difference in the risk of stroke or systemic embolism between ximelagatran (2.5%) and warfarin (2.5%; Box 1). In both trials, findings for ximelagatran fulfilled the criterion for non-inferiority.

However, the pooled results of the SPORTIF trials also showed that ximelagatran significantly *reduced the risk of major bleeding* compared with warfarin (2.5% for ximelagatran; 3.4% for warfarin; estimated annualised ARR, 0.6%; NNT for 1 year to avoid one major bleed, 167) and *increased the risk of transiently elevated levels of liver alanine aminotransferase (ALT) enzymes* (6.1% for ximelagatran; 0.8% for warfarin; absolute risk increase [ARI], 5.3%; number of patients needed to treat with ximelagatran to harm [NNH] with increased ALT, 19). Raised ALT levels typically occurred 2–6 months after initiation of ximelagatran therapy, but produced no symptoms, were transient (returning to baseline spontaneously or after cessation of treatment), and without sequelae in all cases reported in the SPORTIF trials.

These results suggest the beginning of the end of warfarin, because ximelagatran is not only associated with less major bleeding than warfarin, but it also has a predictable pharmacokinetic profile (uninfluenced by the patient's age, sex, weight, ethnicity or diet). Therefore, it is not necessary to monitor anticoagulation activity or adjust the dose of ximelagatran (except in patients with renal dysfunction, in whom a decrease in dose or longer dosing interval is likely to be required). Furthermore, ximelagatran has a wider therapeutic margin than warfarin, and a low potential for drug interactions (Box 2). Although the cost of ximelagatran is likely to be substantially higher than the cost of warfarin, it may prove to be more cost effective because of its lower risk

of bleeding and superior convenience (eg, no laboratory monitoring).

Yet, important questions remain. First, there was significant heterogeneity between the two SPORTIF trials ($P=0.02$). In the SPORTIF III trial, random allocation to open-label ximelagatran was associated with an absolute reduction in stroke or systemic embolism of 0.7% per year compared with warfarin, whereas in the SPORTIF V trial allocation to double-blinded ximelagatran was associated with an absolute increase in stroke or systemic embolism of 0.4% per year compared with warfarin. The cause of this heterogeneity remains uncertain, but might, at least in part, be accounted for by diagnostic suspicion or reporting bias in the open-label SPORTIF III trial. Second, the 2% per year threshold that was chosen as the criterion for non-inferiority does not reliably exclude even a near doubling of risk of stroke or systemic embolism with ximelagatran compared with warfarin. Third, unexpected hepatic side-effects of ximelagatran are an important concern given their high incidence in the short-term (6%), the large population potentially eligible for ximelagatran, and the likely long-term exposures to ximelagatran (and possibility of other long-term adverse effects). Monitoring of liver function is likely to be required during the first 6 months of treatment, and additional long term outcome data are required.

The SPORTIF data signal the emergence of ximelagatran as an effective, safe and more convenient long-term alternative to warfarin for preventing stroke in patients with non-valvular atrial fibrillation. Safety concerns and cost issues are likely to delay its approval and eventual uptake by clinicians in Australia. In the meantime a range of other new antithrombotic drugs are also being evaluated for this indication. Both idraparinax (a selective clotting factor Xa inhibitor administered by once-weekly subcutaneous injection) and the combination of aspirin and clopidogrel are being tested in clinical trials, and novel oral preparations of direct-thrombin inhibitor and factor Xa inhibitors are in

clinical development. This is heartening news for patients with atrial fibrillation, their doctors, and also public health professionals and governments faced with a looming epidemic of morbidity caused by atrial fibrillation in the ageing Australian community.

John W Eikelboom

Haematologist, Royal Perth Hospital, Perth, WA, and
Senior Lecturer, School of Medicine and Pharmacology
University of Western Australia
john.eikelboom@health.wa.gov.au

Graeme J Hankey

Neurologist, and Head of Stroke Unit, Royal Perth Hospital, Perth, WA, and
Clinical Professor, School of Medicine and Pharmacology
University of Western Australia

Competing interests: Graeme Hankey is a member of the Steering Committee of the AMADEUS trial, the Stroke Advisory Committee of the ACTIVE trial, and the Atrial Fibrillation Advisory Board for Exanta, AstraZeneca, Australia.

- Hart RG, Halperin JL, Pearce LA, et al. Lessons from the Stroke Prevention in Atrial Fibrillation Trials. *Ann Intern Med* 2003; 138: 831-838.
- Lake FR, Cullen KJ, de Klerk NH, et al. Atrial fibrillation and mortality in an elderly population. *Aust N Z J Med* 1989; 19: 321-326.
- Thrift AG, Dewey HM, Macdonell RAL, et al. Incidence of the major stroke subtypes: initial findings from the North East Melbourne Stroke Incidence Study (NEMESIS). *Stroke* 2001; 32: 1732-1738.
- Hart RG, Benavente O, McBride R, Pearce LA. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Intern Med* 1999; 131: 492-501.
- Hirsh J, Dalen JE, Anderson DR, et al. Oral anticoagulants: mechanism of action, clinical effectiveness, and optimal therapeutic range. *Chest* 2001; 119 (1 Suppl): 8S-21S.
- Go AS, Hylek EM, Chang Y, et al. Anticoagulation therapy for stroke prevention in atrial fibrillation: how well do randomised trials translate into clinical practice? *JAMA* 2003; 290: 2685-2692.
- Hylek EM, Go AS, Chang Y, et al. Effect of intensity of oral anticoagulation on stroke severity and mortality. *N Engl J Med* 2003; 349: 1019-1026.
- SPORTIF III Investigators. Stroke prevention with the oral direct thrombin inhibitor Ximelagatran compared with warfarin in patients with non-valvular atrial fibrillation (SPORTIF III): randomised controlled trial. *Lancet* 2003; 362: 1691-1698.
- The Executive Steering Committee on behalf of the SPORTIF V investigators. Stroke prevention using the oral direct thrombin inhibitor Ximelagatran in patients with nonvalvular atrial fibrillation (SPORTIF V). Late-breaking clinical trial abstracts [abstract]. *Circulation* 2003; 108: 2.
- Halperin JL. Ximelagatran compared with warfarin for prevention of thromboembolism in patients with nonvalvular atrial fibrillation: rationale, objectives, and design of a pair of clinical studies and baseline patient characteristics (SPORTIF III and V). *Am Heart J* 2003; 146: 431-438. □